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Altered resting-state functional connectivity of the amygdala in Chinese earthquake survivors

Xiaoyu Zhang [a,b], Jianxin Zhang [a], Li Wang [a], Rui Li [a], Wencai Zhang [a,*]

[a] Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences (CAS), No 16 LinCui Road, Chaoyang District, Beijing 100101, China
[b] University of Chinese Academy of Sciences (UCAS), No 380 Huaibei Town, Huairou District, Beijing 101408, China

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ABSTRACT

Posttraumatic stress disorder (PTSD) is linked to abnormal amygdala activities. This study measured amygdala functional connectivity using DSM-5 criteria. There were 33 participants in the PTSD group and 33 participants in a trauma-exposed control (TEC) group, who did not have PTSD according to the PTSD checklist of the DSM-5 (PCL-5). Our findings are as follows: (1) In the PTSD group, the amygdala had increased positive connectivity with the medial prefrontal cortex (mPFC) and hippocampus, and decreased positive connectivity with the inferior mPFC and insula. The amygdala had increased negative connectivity with the orbital prefrontal cortex and decreased negative connectivity with the insula in comparison with TEC group. (2) PCL of all participants was correlated with the connectivity between the amygdala and the mPFC, hippocampus, and insula. These regions overlapped with those identified in the between-group comparisons. However, there was no association between PCL of the PTSD group and connectivity in these regions. Abnormal functional connectivity between the amygdala and mPFC subdivisions, hippocampus, and insula reveals their importance in PTSD pathogenesis.

1. Introduction

Posttraumatic stress disorder (PTSD) is prevalent among earthquake survivors. The symptom criteria in the recently released DSM-5 include four clusters—intrusion, avoidance, negative alterations in mood and cognitions, and hyperarousal (APA, 2013); these differ from those in the DSM-IV-TR, which categorized criteria into three clusters: intrusion, effortful avoidance and emotional numbing, and hyperarousal. Recent research found that of 221 soldiers with complete data who met the DSM-IV-TR criteria, 67 (30%) did not meet the DSM-5 criteria, and 59 additional soldiers met only the DSM-5 criteria (Hoge et al., 2014). Therefore, it is important to observe the neural mechanisms of PTSD according to the DSM-5 criteria.

The amygdala is a key brain region in fear processing in animals and humans (Hartley and Phelps, 2010). Specifically, the amygdala produces an exaggerated response to fearful and traumatic stimuli and shows increased resting-state activation in PTSD (Hughes and Shin, 2011). It has been found that the amygdala has bidirectional anatomical connections with mPFC (Ray and Zald, 2012) and hippocampus regions (Fanselow and Dong, 2010; Kheirbek and Hen, 2011), constituting the structural foundation by which their activations could influence each other. Further, the neurocircuitry model of PTSD hypothesizes hyperresponsivity within the amygdala to threat-related stimuli, with inadequate top-down governance over the amygdala by vmPFC and the hippocampus (Rauch et al., 2006).

Functional connectivity is a measure of the level of activation synchronization between two or more brain regions as inferred from common changes in their activation over time (Admon et al., 2013). Resting-state connectivity offers a powerful way to assess inherent connections between brain networks (Shimony et al., 2009). Considering the important role of the amygdala in the neurocircuitry of PTSD, and of resting-state functional connectivity, the present study investigated altered resting-state functional connections of the amygdala in PTSD. To date, few studies have examined how abnormalities in resting-state amygdala functional connectivity correspond to DSM-5 criteria.

A limited number of PTSD studies have examined abnormal functional connectivity of the amygdala in task engagement (Fonzo et al., 2010) and in the resting state (Brown et al., 2014; Sripada et al., 2012; Yan et al., 2014). However, results regarding the relationship between the amygdala and ventral medial prefrontal cortex (vmPFC) are inconsistent. For example, two studies found decreased resting-state amygdala functional connectivity with the middle frontal and cingulate cortices (Yan et al., 2014) and the inferior frontal cortex (Brown et al., 2014). The neurocircuitry model of PTSD hypothesizes hyperresponsivity within the amygdala and inadequate top-down governance over the amygdala by vmPFC. This inadequate influence of the vmPFC underlies deficits of extinction, as well as in the capacity to suppress attention and responses to trauma-related stimuli (Rauch et al., 2006). Thus, it has been suggested that a hyperresponsive amygdala accompanied by a hyporesponsive vmPFC or reduced functional connectivity between the two regions in

* Corresponding author.
E-mail address: zhangwc@psych.ac.cn (W. Zhang).

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PTSD could reflect the invalid suppression of vmPFC signals to the amygdala (Hughes and Shin, 2011). In contrast, studies report increased resting-state functional connectivity between the basolateral amygdala (BLA) and the pregenual anterior cingulate cortex (pACC) and dorsomedial prefrontal cortex (Brown et al., 2014), reduced anticorrelation (i.e., negative connectivity) between the amygdala and dorsal and rostral anterior cingulate cortex (ACC) (Sripada et al., 2012), and increased functional connectivity between the amygdala and subgenual ACC during task engagement (Fonzo et al., 2010). Therefore, it is thought that the amygdala and vmPFC may have similar roles in the expression of negative emotions and retrieval of fear memories (Myers-Schulz and Koenigs, 2012; Nieuwenhuis and Takashima, 2011). Hayes et al. (2012) noted that the vmPFC is not a single entity, rather it is composed of multiple distinct regions (i.e., subgenual and perigenual anterior cingulate cortex) that serve a variety of functions.

Similar inconsistencies in functional connectivity appear to apply to the hippocampus. The hippocampus has a bidirectional connection with the amygdala, which serves as a foundation for functional contact (Fanselow and Dong, 2010; Kheirbek and Hen, 2011). Many studies have found enhanced amygdala functional connectivity with the hippocampus in a traumatic exposure task or in a rest state (Cisler et al., 2014; Osuch et al., 2008; Yan et al., 2014), or enhanced hippocampus activation at rest in PTSD (Sachinvala et al., 2000). However, few studies have shown reduced functional connectivity between the amygdala and hippocampus (Sripada et al., 2012; Strafford et al., 2014), or reduced hippocampus glucose absorption at rest in PTSD (Molina et al., 2010). It is evident that more data is required to clarify the functional connectivity between the amygdala and vmPFC and hippocampus in PTSD, and to find reliable neural markers for the diagnosis of PTSD.

The present study addressed two questions. (1) What are the differences in amygdala functional connectivity between PTSD group and trauma-exposed control group without PTSD (TEC group)? In particular, what disease-related brain activities in the vmPFC and hippocampus can be observed when comparing PTSD and TEC groups. (2) What characteristics of functional connectivity are correlated with symptom severity in PTSD? In comparison with previous studies, updated DSM-5 criteria and a larger sample size were used to distinguish the PTSD group and TEC group among earthquake survivors.

2. Methods

2.1. Participants

All participants were recruited from Mianzhu City, Sichuan province, which was destroyed by the 2008 Wenchuan Earthquake. Seventy-one participants aged 38–62 years were recruited. They had no major psychosis (e.g., schizophrenia and organic mental disorders), significant head injury, or drug or alcohol abuse.

All were assessed with the PTSD Checklist for DSM-5 (PCL-5) (Blevins et al., 2012), the Center for Epidemiologic Studies Depression Scale (CES-D) (Wang et al., 2015), and a trauma exposure questionnaire (Liu et al., 2014). The CES-D is used to assess depression symptoms. It is a self-report scale of 20 items, reflecting depressed mood, feelings of guilt or worthlessness, perceptions of helplessness or hopelessness, and psychomotor–somatic symptoms. The CES-D has been validated and widely used in Chinese populations (Cheung and Bagley, 1998). The self-report trauma exposure questionnaire was used to quantify the extent of trauma exposure after the earthquake. Participants answered yes/no questions regarding post-earthquake events with different levels of associated trauma. The study procedures were approved by the Institute of Psychology, Chinese Academy of Sciences. All subjects gave written informed consent to take part in the experiment.

Thirty-five participants meeting the criteria for PTSD were assigned to the trauma-exposed PTSD group (PTSD group), and the remaining 36 participants were assigned to the trauma-exposed control group (TEC group). Five participants were excluded because of head motion in the fMRI analysis, resulting in 66 participants (33 in the PTSD group and 33 in the TEC group) entering the final analysis.

2.2. Data acquisition

Scans were acquired on a 1.5 T Philips Achieva Scanner. After participants were positioned in the scanner, a T1-weighted low-resolution structural image was aligned approximately parallel to the anterior callosum–posterior callosum line. Thirty transverse slices of resting-state functional images that covered the whole brain were acquired with a T2-weighted echo-planar imaging sequence based on blood oxygenation level-dependent (BOLD) contrast (repetition time = 3000 ms, echo time = 30 ms, flip angle = 90°, field of view = 220 × 220 mm^2, matrix = 256 × 256, slice thickness = 4 mm, slice gap = 0 mm, voxel size = 3.44 × 3.44 × 4 mm^3). The scan duration was 8 min (160 TRs). Throughout the scanning procedure, participants were instructed to close their eyes, remain awake, and maintain immobility, especially for the head. After the resting-state scan, a high-resolution anatomical T1-weighted image was acquired to aid registration (repetition time = 8.5 ms, echo time = 3.74 ms, flip angle = 8°, field of view = 220 × 220 mm^2, matrix = 220 × 200, slices = 180, voxel size = 1 × 1 × 1 mm^3, slice gap = 0, slice orientation = sagittal).

2.3. Preprocessing of fMRI data

Functional MRI preprocessing and statistical analyses were conducted using Resting-State fMRI (DPARSF V2.3, by YAN Chao-Gan, http://www.restfmri.net), which is based on MRIcroN (by Chris Rorden, http://www.mricro.com), statistical parametric mapping (SPM8; Wellcome Department of Imaging Neuroscience, London, UK), and the Resting-State fMRI Data Analysis Toolkit (REST V1.8 software, by SONG Xiao-Wei et al., http://www.restfmri.net). The first 10 TRs of each functional time series were discarded accounting for magnetic field stabilization, and the remaining 150 TRs were preprocessed. The images were subsequently corrected for slice timing and realigned to the first image for rigid-body head movement correction (5 participants with head motion of more than 2.5 mm of maximum displacement in any direction (x, y or z) or 2.5° of angular motion were excluded from further analysis). The functional images were normalized into a standard stereotaxic anatomical Montreal Neurological Institute space. The normalized volumes were resampled to a voxel size of 3 × 3 × 3 mm^3. Echo-planar images were spatially smoothed using an isotropic Gaussian filter of 8 mm full width at half maximum. Each voxel's time-series was detrended to correct for lineal drift over time. Following this procedure, temporal filtering (0.01 Hz–0.08 Hz) was applied to the time series of each voxel to reduce the effect of low-frequency drift and high-frequency noise. Nine nuisance covariates (time-series predictors for global signal, white matter, cerebrospinal fluid, and the six movement parameters, including the first derivative, obtained during realignment to account for motion-related effects in blood oxygenated level-dependent) were sequentially regressed from the time-series.

2.4. Data analysis

The anatomical amygdala ROI was defined by WFU-Pick Atlas Tool version 3.0.3 (http://fmri.wfubmc.edu/software/PickAtlas). Left and right amygdala were separately selected as two seed regions. Then the data analyses were carried out according to the following steps.

Firstly, correlation coefficients were computed between the time series of the amygdala and that of all the other brain voxels consecutively. Correlation coefficients were then translated into Z values using Fisher's z-transform to improve the normality. Subsequently, Z values generated at an individual level were submitted to a group analysis using a random effects model.

Secondly, Z values of individual levels in the PTSD and TEC groups were separately entered into a one-sample t-test in a voxel-wise